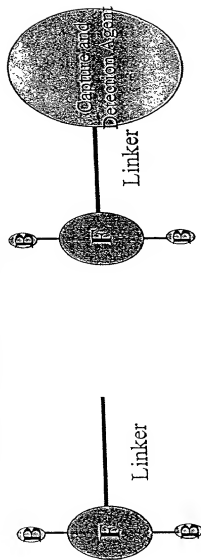


# High-throughput Target ID



## Library of Target ID Compounds

## Library of Bioactive Compounds

Use corresponding activity-based probe to identify the biological target

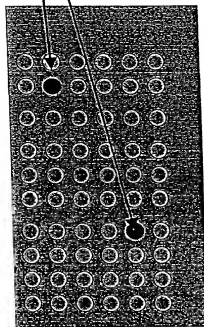
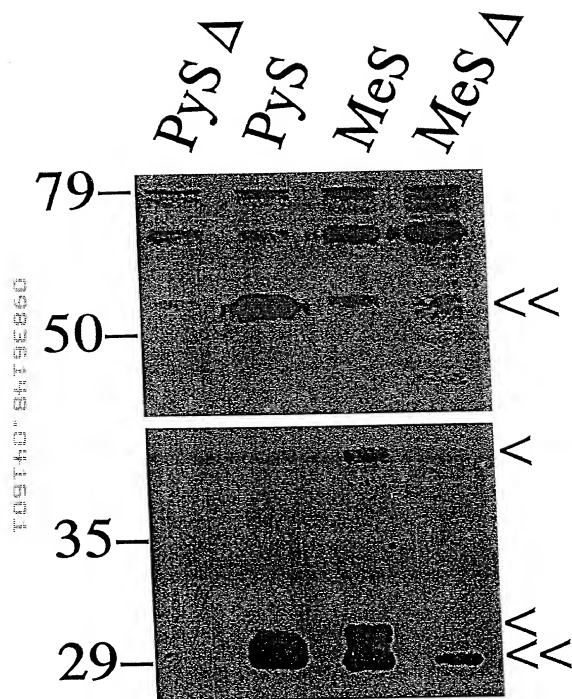


FIGURE 2



# Non-Directed Tagged Library of Sulfonates Identifies Probe for ADH Superfamily of Enzymes

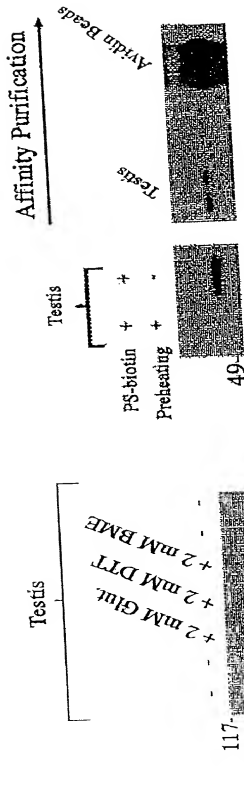


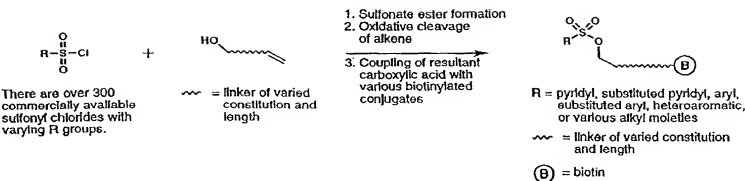
FIGURE 3

• MALDI mapping identifies tagged protein as aldehyde dehydrogenase (ADH, cytosolic class II)

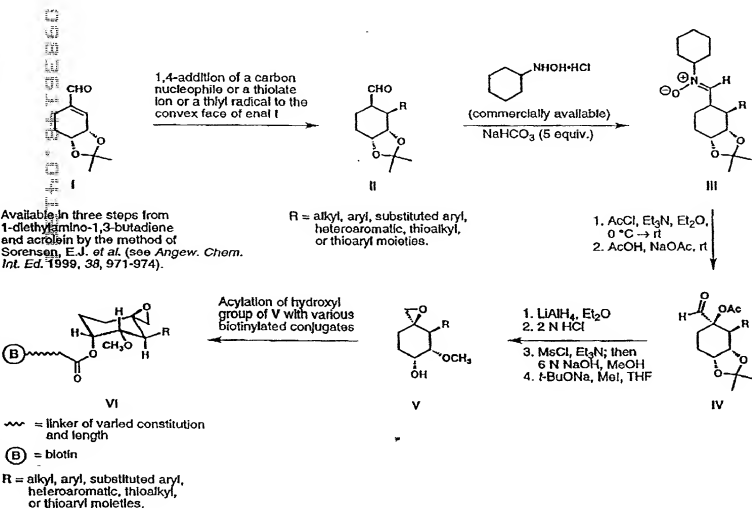
• 28 ADHs in fly genome

- Involved in retinoic acid biosynthesis and catabolism of alcohol and chemotherapeutic agents

FIGURE 4



Scheme 1. A pathway for syntheses of various biotinylated sulfonate esters for use in activity-based proteomics studies.



Scheme 2. A strategy for convergent, stereocontrolled syntheses of conformationally well-defined spiroepoxides of type VI. Literature precedent for I  $\rightarrow$  II  $\rightarrow$  III  $\rightarrow$  IV  $\rightarrow$  V can be found in Sorensen, E.J. *et al. Angew. Chem. Int. Ed.* 1999, 38, 971-974. Compounds of type VI are analogs of the metalloprotease (MetAp-2) inhibitor fumagillin and will be employed as covalent affinity agents in activity-based proteomics studies.

# FP-Biotin: a kinetic reporter of SH Activity

- The rates at which the majority of SHs react with FP-biotin can be experimentally followed
- FP-biotin readily detects low femtomole quantities of SHs directly in complex cell/tissue proteomes

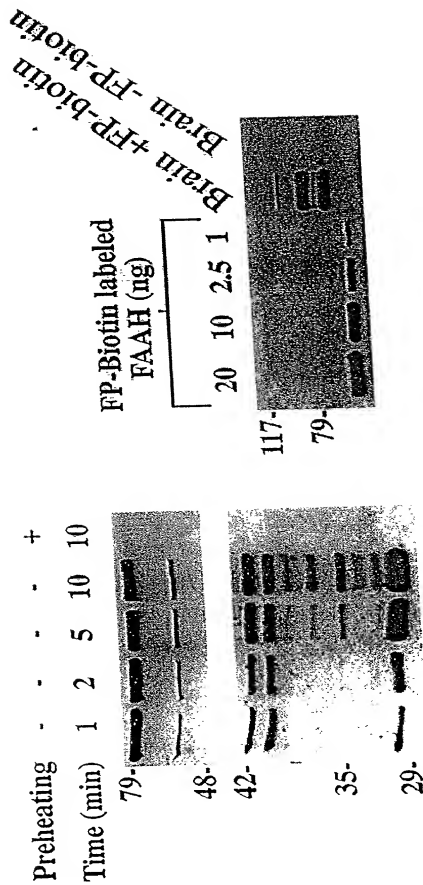


FIGURE 5

# Utility of Multiplexed probes in identifying Serine Hydrolases

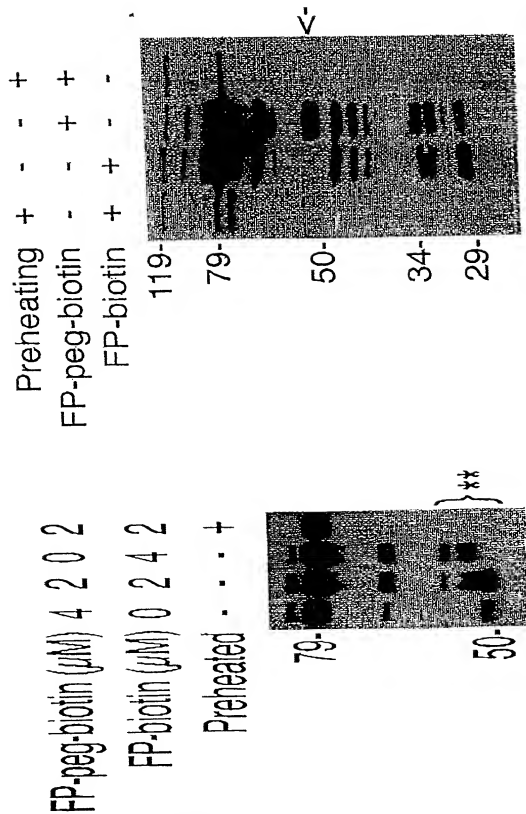
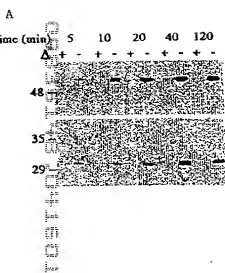


FIGURE 6

FIGURE 7



B

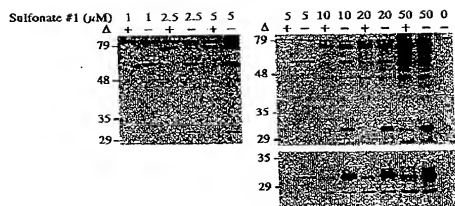
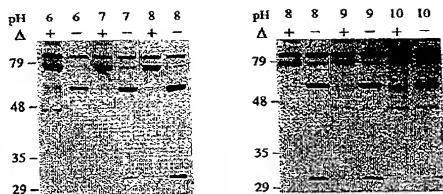


FIGURE 7

C



D

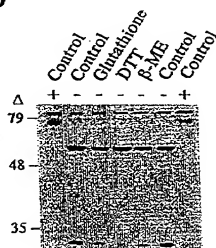




FIGURE 8

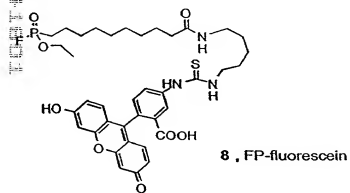
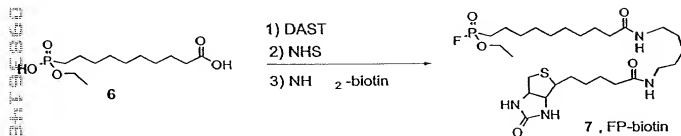
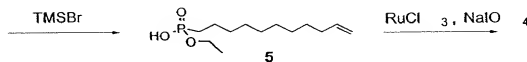
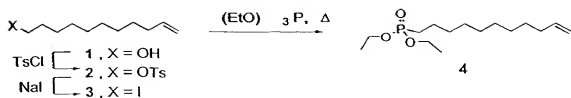


FIGURE 9

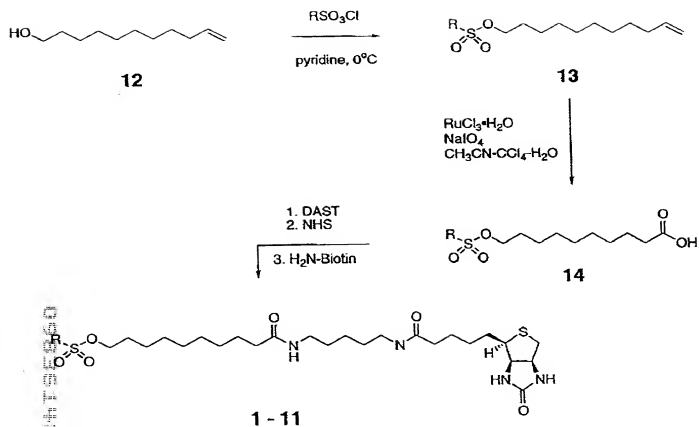
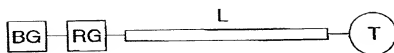


FIGURE 10

A.



B.

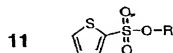
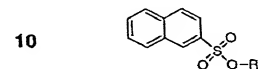
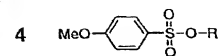
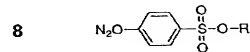
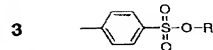
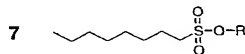
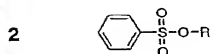
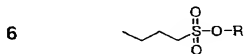
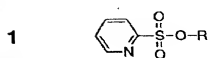
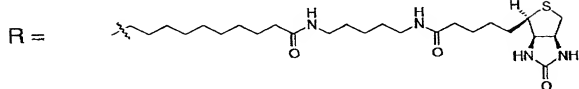
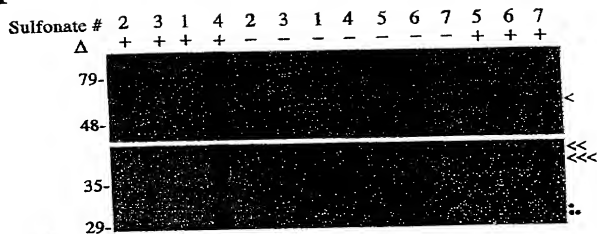


FIGURE 11

A



B

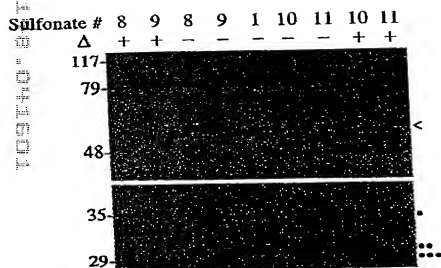
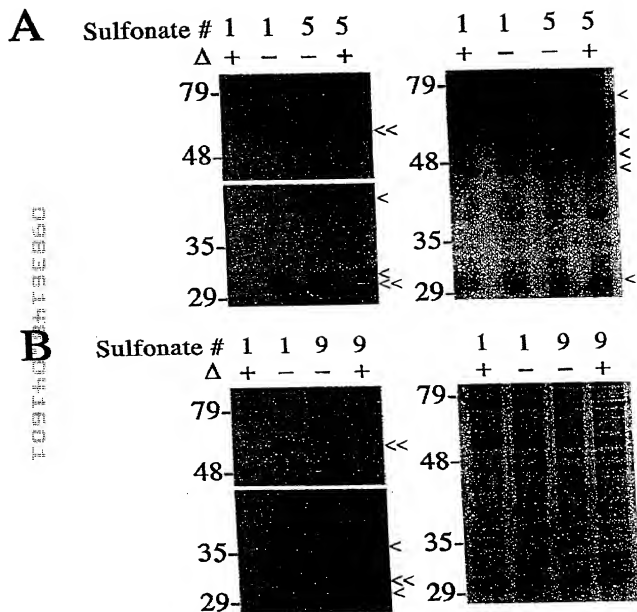
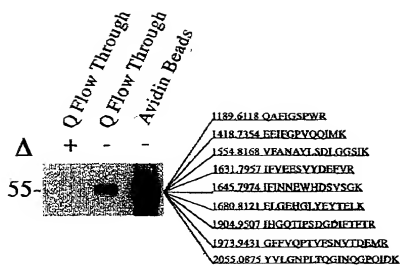


FIGURE 12

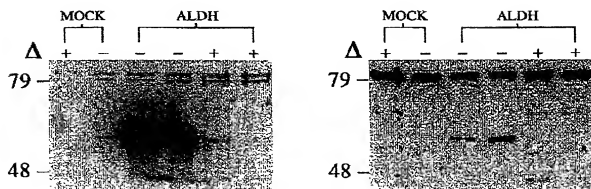


A

FIGURE 13



B



C

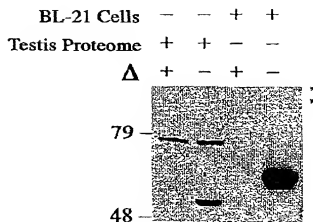
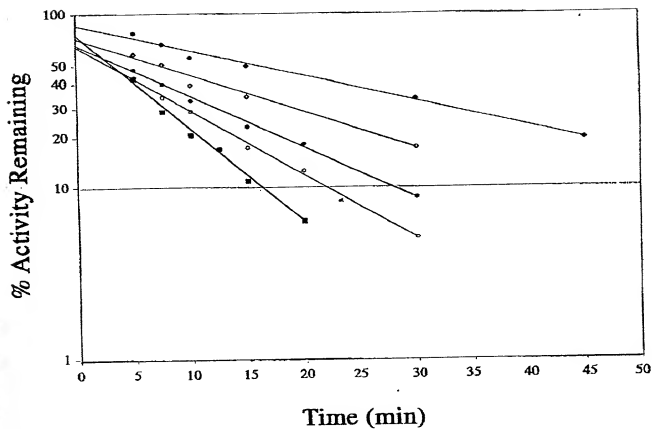


FIGURE 14



**B**

Competitor #	-	-	15	17	16	15	17	16
[Competitor ( $\mu$ M)]	0	0	5	5	5	50	50	50
$\Delta$	+	-	-	-	-	-	-	-

79

48

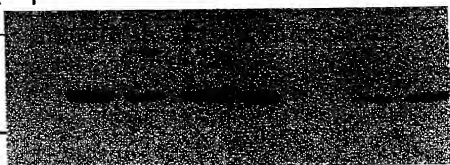
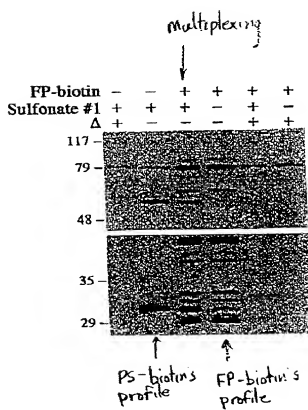


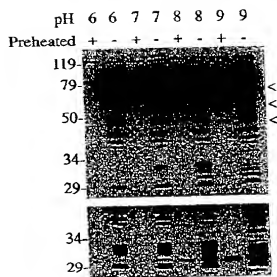
FIGURE 15



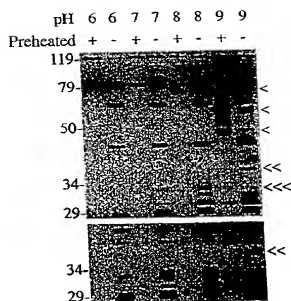
109140" 84192260



FIGURE 16



FP-peg-biotin



FP-biotin

10440-373600

FIGURE 17

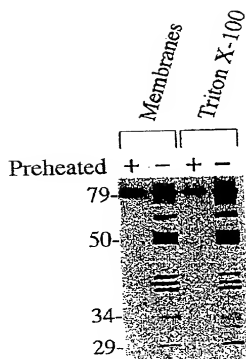
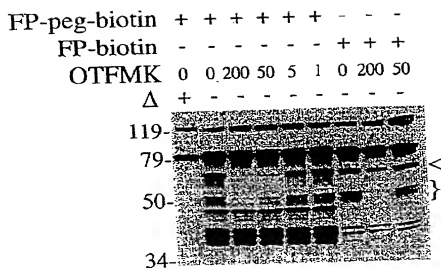


FIGURE 18



100110" 241922222

FIGURE 19

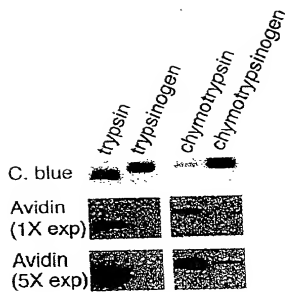


FIGURE 20

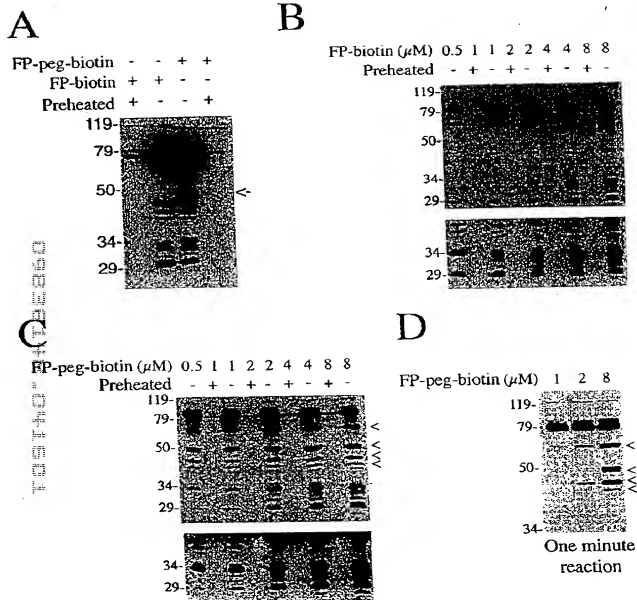


FIGURE 21

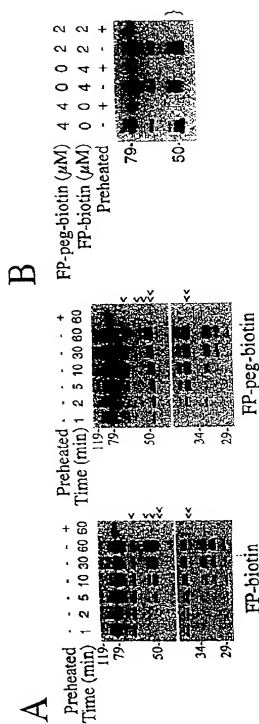




FIGURE 23

